Medical Policy
Cytochrome P450 Genotype-Guided Treatment Strategy

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Policy Number: 256
BCBSA Reference Number: 2.04.38
NCD/LCD: Local Coverage Determination (LCD): MolDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing (L35072)

Related Policies
- Genetic Testing for Mental Health Conditions, #669
- Genetic Guided Tamoxifen Treatment, #67
- Genetic testing for Warfarin Dose, #214
- Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines, #096

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

CYP450 genotyping for the purpose of aiding in the choice of clopidogrel vs alternative antiplatelet agents, or in decisions on the optimal dosing for clopidogrel, may be considered INVESTIGATIONAL.

CYP2D6 genotyping to determine drug metabolizer status may be considered MEDICALLY NECESSARY for patients:
- With Gaucher disease being considered for treatment with eliglustat; OR
- With Huntington disease being considered for treatment with tetrabenazine in a dosage greater than 50 mg per day.

CYP450 genotyping for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity for the following drugs is considered INVESTIGATIONAL, aside from determinations in the separate policies noted above.
- Selection or dosage of codeine
- Dosing of efavirenz and other antiretroviral therapies for HIV infection
- Dosing of immunosuppressant for organ transplantation
- Selection or dosing of beta blockers (eg, metoprolol)
- Dosing and management of anti-tuberculosis medications.
The use of genetic testing panels that include multiple CYP450 variants is considered INVESTIGATIONAL.

**Medicare HMO BlueSM and Medicare PPO BlueSM Members**

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

**Local Coverage Determination (LCD): MolDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing (L35072)**

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

**Prior Authorization Information**

**Inpatient**
- For services described in this policy, precertification/preauthorization IS REQUIRED for all products if the procedure is performed inpatient.

**Outpatient**
- For services described in this policy, see below for products where prior authorization might be required if the procedure is performed outpatient.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Prior authorization is not required.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>Prior authorization is not required.</td>
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<tr>
<td>Medicare HMO BlueSM</td>
<td>Prior authorization is not required.</td>
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<tr>
<td>Medicare PPO BlueSM</td>
<td>Prior authorization is not required.</td>
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</table>

**CPT Codes / HCPCS Codes / ICD Codes**

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

**CPT Codes**

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT codes above if medical necessity criteria are met:
**ICD-10 diagnosis coding**

<table>
<thead>
<tr>
<th>ICD-10-cm diagnosis codes:</th>
<th>code description</th>
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<tbody>
<tr>
<td>E75.22</td>
<td>Gaucher disease</td>
</tr>
<tr>
<td>G10</td>
<td>Huntington's disease</td>
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</tbody>
</table>

The following CPT codes are considered investigational for **Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:**

**CPT Codes**

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81230</td>
<td>CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22)</td>
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</tbody>
</table>

**Description**

**DRUG EFFICACY AND TOXICITY**

Drug efficacy and toxicity vary substantially across individuals. Because drugs and doses are typically adjusted, if needed, by trial-and-error, clinical consequences may include a prolonged time to optimal therapy. In some cases, serious adverse events may result.

Multiple factors may influence the variability of drug effects, including age, liver function, concomitant diseases, nutrition, smoking, and drug-drug interactions. Inherited (germline) DNA sequence variation in genes coding for drug-metabolizing enzymes, drug receptors, drug transporters, and molecules involved in signal transduction pathways also may have major effects on the activity of those molecules and thus on the efficacy or toxicity of a drug.

Pharmacogenomics studies how an individual’s genetic inheritance affects the body’s response to drugs. It may be possible to predict therapeutic failures or severe adverse drug reactions in individual patients by testing for important DNA variants (genotyping) in genes related to the metabolic pathway (pharmacokinetics) or signal transduction pathway (pharmacodynamics) of the drug. Potentially, test results could be used to optimize drug choice and/or dose for more effective therapy, avoid serious adverse events, and decrease medical costs.

**CYTOCHROME P450 SYSTEM**

The cytochrome P450 (CYP450) family is a major subset of all drug-metabolizing enzymes; several CYP450 enzymes are involved in the metabolism of a significant proportion of currently administered drugs. CYP2D6 metabolizes approximately 25% of all clinically used medications (eg, dextromethorphan, β-blockers, antiarrhythmics, antidepressants, morphine derivatives), including most prescribed drugs. CYP2C19 metabolizes several important types of drugs, including proton pump inhibitors, diazepam, propranolol, imipramine, and amitriptyline.

Some CYP450 enzymes are highly polymorphic, resulting in some enzyme variants that have variable metabolic capacities among individuals, and some with little to no impact on activity. Thus, CYP450 enzymes constitute an important group of drug-gene interactions influencing the variability of the effect of some CYP450-metabolized drugs.

Individuals with 2 copies (alleles) of the most common (wild-type) DNA sequence of a particular CYP450 enzyme gene resulting in an active molecule are termed extensive metabolizers (EMs; normal). Poor metabolizers (PMs) lack active enzyme gene alleles, and intermediate metabolizers, who have 1 active and 1 inactive enzyme gene allele, may experience to a lesser degree some of the consequences of
PMs. Ultrarapid metabolizers (UMs) are individuals with more than 2 alleles of an active enzyme gene. There is pronounced ethnic variability in the population distribution of metabolizer types for a given CYP enzyme.

UMs administered an active drug may not reach therapeutic concentrations at usual recommended doses of active drugs, while PMs may suffer more adverse events at usual doses due to reduced metabolism and increased concentrations. Conversely, for administered prodrugs that must be converted by CYP450 enzymes into active metabolites, UMs may suffer adverse events, and PMs may not respond.

Many drugs are metabolized to varying degrees by more than 1 enzyme, either within or outside of the CYP450 superfamily. Also, the interaction between different metabolizing genes, the interaction between genes and environment, and interactions among different nongenetic factors also influence CYP450-specific metabolizing functions. Thus, identification of a variant in a single gene in the metabolic pathway may be insufficient in all but a small proportion of drugs to explain interindividual differences in metabolism and consequent efficacy or toxicity.

DETERMINING GENETIC VARIABILITY IN DRUG RESPONSE
Genetically determined variability in drug response has been traditionally addressed using a trial-and-error approach to prescribing and dosing, along with therapeutic drug monitoring for drugs with a very narrow therapeutic range and/or potentially serious adverse events outside that range. However, therapeutic drug monitoring is not available for all drugs of interest, and a cautious trial-and-error approach can lengthen the time to achieving an effective dose.

CYP450 enzyme phenotyping (identifying metabolizer status) can be accomplished by administering a test enzyme substrate to a patient and monitoring parent substrate and metabolite concentrations over time (eg, in urine). However, testing and interpretation are time-consuming and inconvenient; as a result, phenotyping is seldom performed.

The clinical utility of CYP450 genotyping (ie, the likelihood that genotyping will significantly improve drug choice, dosing, and patient outcomes) may be favored when the drug under consideration has a narrow therapeutic dose range, when the consequences of treatment failure are severe, and/or when serious adverse reactions are more likely in patients with gene sequence variants. Under these circumstances, genotyping may direct early selection of the most effective drug or dose, and/or avoid drugs or doses likely to cause toxicity. For example, warfarin, some neuroleptics, and tricyclic antidepressants have narrow therapeutic windows and can cause serious adverse events when concentrations exceed certain limits, resulting in cautious dosing protocols. The potential severity of the disease condition may call for immediate and sufficient therapy; genotyping might speed up the process of achieving a therapeutic dose and avoiding significant adverse events.

Summary
The cytochrome P450 (CYP450) family is involved in the metabolism of many currently administered drugs, and genetic variants in cytochrome P450 are associated with altered metabolism of many drugs. Testing for cytochrome P450 variants may assist in selecting and dosing drugs affected by these genetic variants.

Clopidogrel
For individuals with a need for antiplatelet therapy who are undergoing or being considered for clopidogrel therapy who receive a CYP2C19-guided treatment strategy, the evidence includes 2 randomized controlled trials (RCTs). Relevant outcomes are overall survival, medication use, and treatment-related morbidity. The 2 RCTs evaluated the impact of CYP2C19 genotyping using an intermediate outcome measure (platelet reactivity). One RCT showed no statistical difference between patients with on-treatment high platelet reactivity between genotype-guided management or standard treatment with clopidogrel. The second RCT showed carriers of loss of function alleles did not respond to augmented clopidogrel as well as they did to prasugrel, and physician-directed clopidogrel was effective for most noncarriers. However, routine testing using platelet reactivity as an outcome measure to predict CYP2C19 metabolic state has not been shown to improve health outcomes. Results of an ongoing RCT
(TAILOR-PCI), assessing outcomes in 5270 patients randomized to genotype-based antiplatelet therapy approach or standard care, are expected in 2020 and likely to address this gap. The evidence is insufficient to determine the effects of the technology on health outcomes.

Other Drugs
For individuals who are undergoing or being considered for treatment with highly active antiretroviral agents, immunosuppressant therapy for organ transplantation, beta-blockers, or antitubercular medications who receive a CYP2C19-guided treatment strategy, the evidence includes retrospective studies. Relevant outcomes are medication use and treatment-related morbidity. In general, most published CYP450 pharmacogenomic studies for these drugs consist of retrospective evaluations of CYP450 genotype associations, reporting intermediate outcomes (eg, circulating drug concentrations) or less often, final outcomes (eg, adverse events or efficacy). Many of these studies are small, underpowered and hypothesis generating. Prospective intervention studies, including RCTs documenting the clinical usefulness of CYP450 genotyping to improve existing clinical decision making to guide dose or drug selection, which may then translate into improvement in patient outcomes, were not identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>11/2018</td>
<td>BCBSA National medical policy review. Four criteria removed from the third investigational statement; the intent of statements otherwise unchanged. Policy title changed. Information on pharmacologic treatments used to treat mental health disorders were removed from this policy and added to policy #669 Genetic Testing for Diagnosis and Management of Mental Health Conditions. Effective 11/1/2018.</td>
</tr>
<tr>
<td>1/2018</td>
<td>Clarified coding information.</td>
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<tr>
<td>8/2017</td>
<td>BCBSA National medical policy review. New references added. Background and summary updated. 8/2017</td>
</tr>
<tr>
<td>5/2016</td>
<td>BCBSA National medical policy review. Medically necessary statements for CYP2B6 genotyping for patients being considered for eliglustat or tetrabenazine therapy added; “for all drugs” statement removed from investigational statement; medical necessary statement for CYP2C19 genotyping for patients receiving clopidogrel therapy changed to investigational. Effective 5/1/2016.</td>
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<td>7/2015</td>
<td>Local Coverage Determination (LCD): MolDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing (L34499) added.</td>
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<tr>
<td>1/2014</td>
<td>New references added from BCBSA National medical policy.</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:

Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
References


